Chronic diabetic complications

Nephropathy, neuropathy, macrovascular complications, diabetic foot syndrome

Diabetes mellitus = chronic metabolic disease

- After many years of duration causes irreversible changes of tissues – the most important changes are found in connective tissues
- ***diabetic microangiopathy*** (retino-, neuro-, nephropathy)
- ***diabetic macroangiopathy*** (CAD, POAD)
- ***changes in connective tissues of joints, tendons and skin***
- = consequence of long-term hyperglycemia action
- Late diabetic syndrome = the leading cause of increased mortality and morbidity in diabetic patients.

Pathogenesis of chronic complications:

- **„glucose toxicity“ =** acute or chronic „side effect“ – the influence of glucose level on cell structure and function
- ***Included:***

- micro a macrovascular complications
- cellular immunity disturbances
- growth and differentiation disturbances of cells
- abnormal carbohydrates metabolism – insulin secretion impairment and insulin resistance caused by hyperglycemia

Mechanisms of hyperglycemia action:

A/ reversible abnormalities

– removable by glucose level normalisation

- polyol´s path
- hemodynamic changes (increasing of hydrostatic pressure in circulation)
- increased activity of proteinkinase C
- increased formation of early glycosylated products

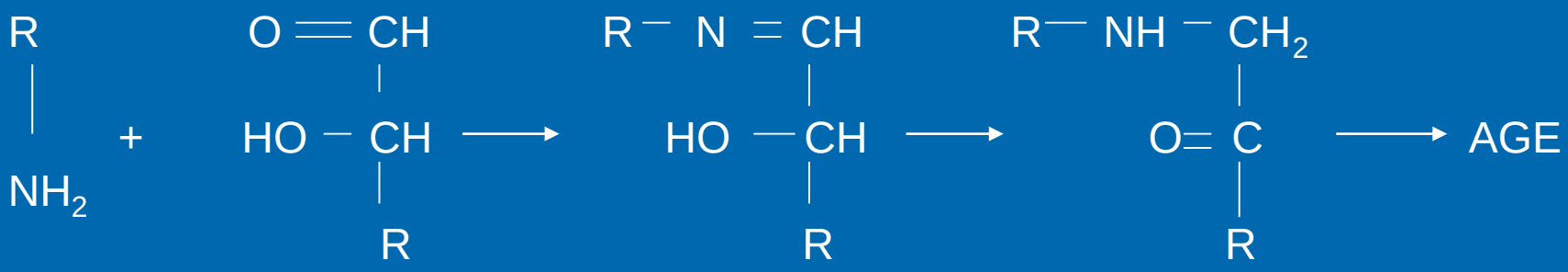
This actions are linked to cell wall permealibity increase and leaking of proteins into extracellular space

B/ irreversible, chronic abnormalities

– irremovable by glucose level normalisation

–„AGE“ products formation (advanced glycated endproducts) = long-lived molecules, originally formed by glycosylation of cell wall components, plasmatic proteins, lipoproteins etc.

These molecules cause changes in structure and function of the tissues and tend to accumulate. Difficult removable.



protein | glucose | aldimin (Schiff´s basis) | ketoamin | advanced glycated endproduct

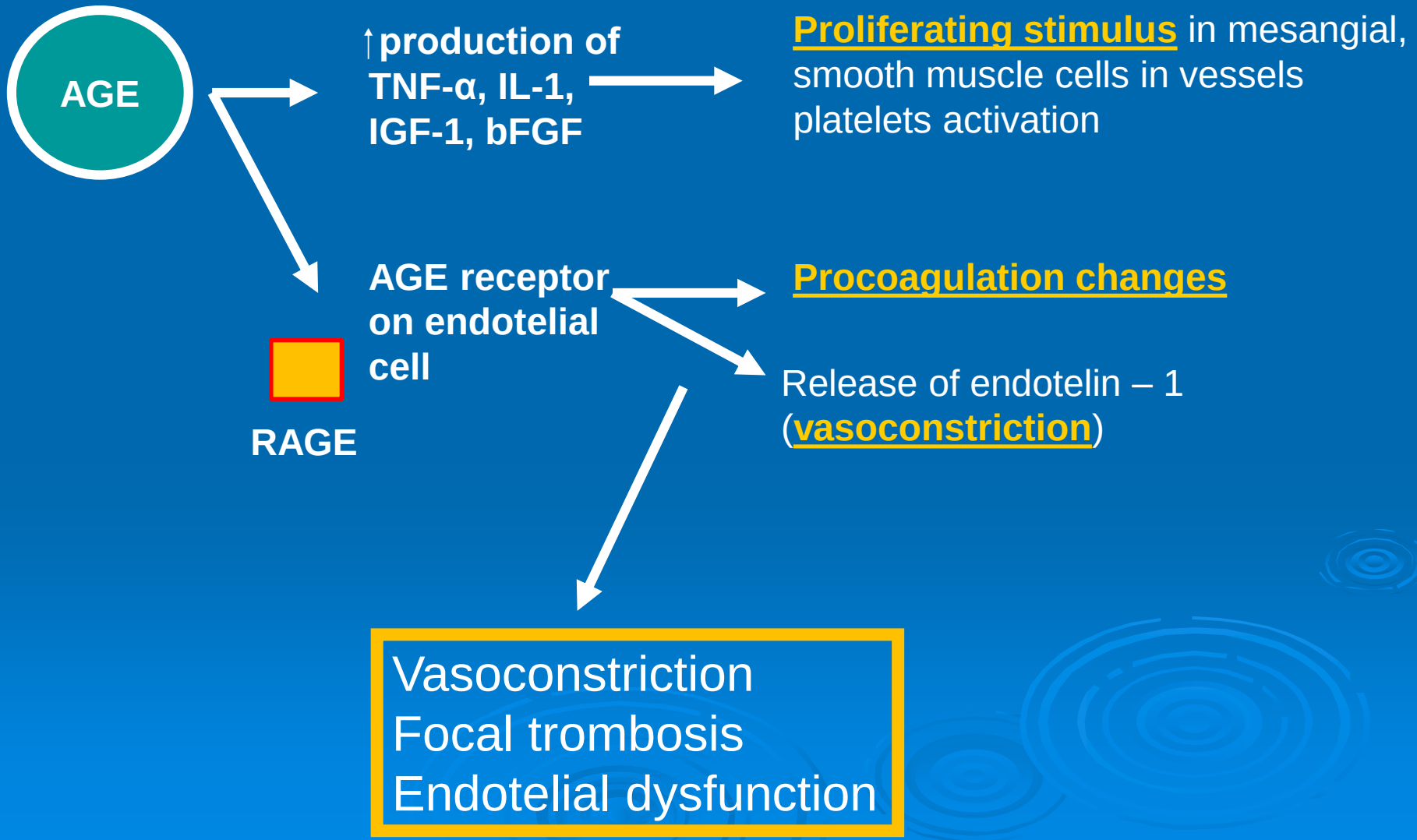
1/ Nonenzymatic glycosylation -

Glucose is incorporated in the proteins with covalent bond, no energy expenditure is needed

AGE products

- Cause functional and structural abnormalities in tissues
- Bind to receptors (RAGE) located on macrophages and endotelial cells
- Could trigger cytokines release that leads to progression of tissue impairment.

NONENZYMATIC GLYCOSYLATION :



Glycosylation of some molecules could be of a ***specific importance:***

-**Colagen** – changes of solidity, elasticity of connective tissues – including the vessel wall.

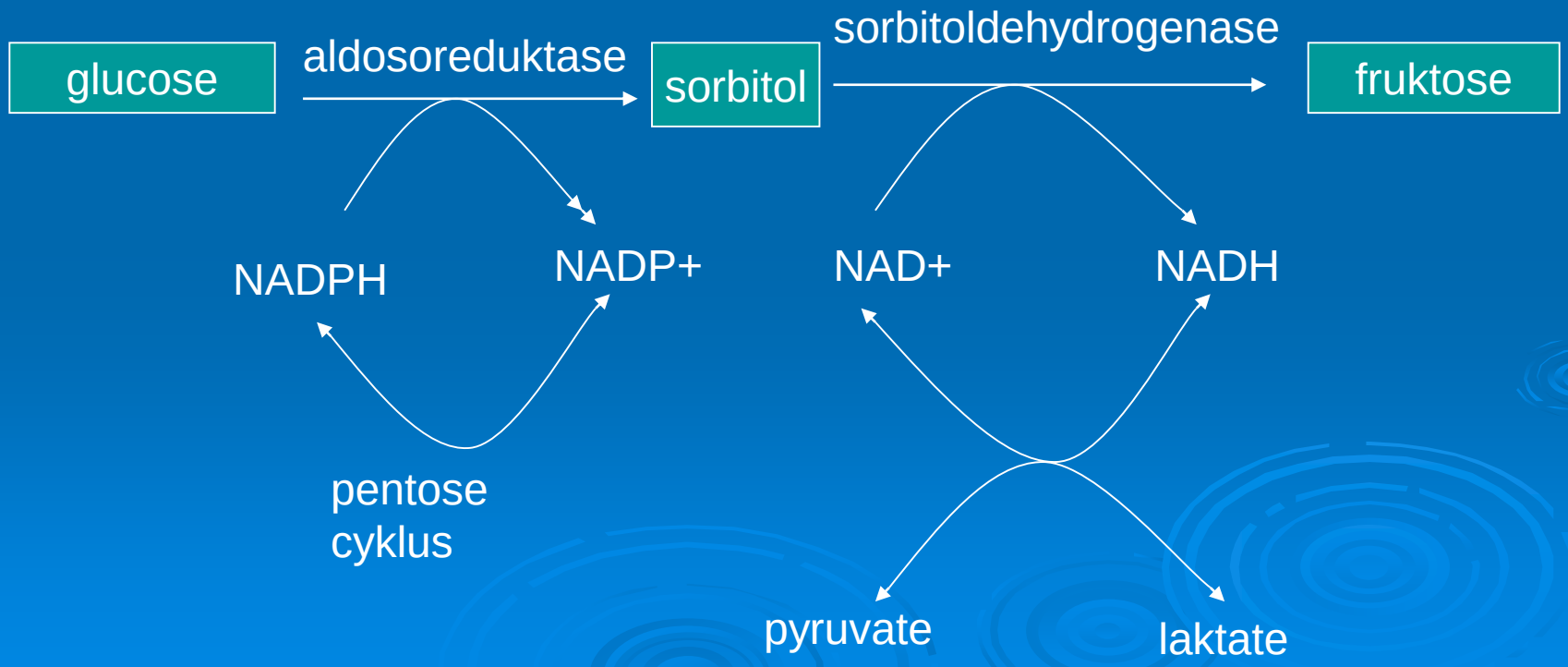
- the electrostatic charge of some molecules is changing, especially of glycosaminglycans in the basement membrane that causes increased permeability
- glycosylation of colagen in the red cell causes decreased deformability of the red cell

-**DNA** – mutations, alterations in gene expression

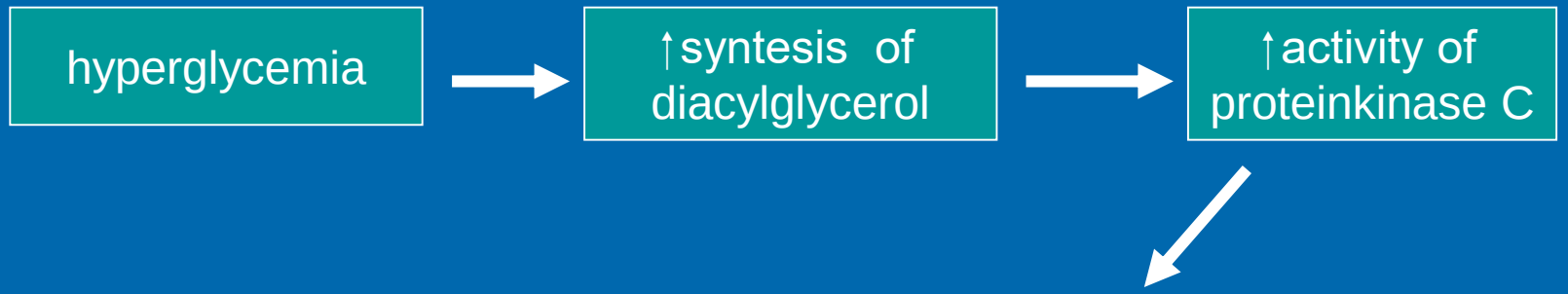
-**LDL cholesterol** – glycosylation releives peroxidation - increase in ROS and is easily to be catched by scavenger receptors of macrophages and easily incorporated into the AS plaque

2/ Polyol´s path:

- sorbitol and NADH cummulate – „diabetic pseudohypoxia“
-Osmotic damage of the cells by the accumulated sorbitol
-Function of Na/K ATPase in nerve tissue = speed of impulse conduction in the nervous tissue is lower than normally



3/ Increased activt of proteinkinase C:



- inhibition of Na/K ATPase – functional impairment of endothelial, nervous cells
- stimulation of colagen IV, fibronectin, TGF, endothelial growth factors production

4/ Free oxygen radicals formation, oxidative stress

Diabetic nephropathy

- = chronic progressive kidney disease in diabetic patients
- in literal meaning any kidney disease in diabetic patients
- of narrow sense - diabetic renal microangiopathy
- clinical syndrome with general vessel disturbances
- Leading sign is proteinuria/microalbuminuria
- MAU forms a indicator of cardiovascular impairment
- in type 1 and 2 diabetic patiets
- Diabetes is responsible for 30-40% of all end-stage renal disease (ESRD)
- great majority of patients are those with type 2

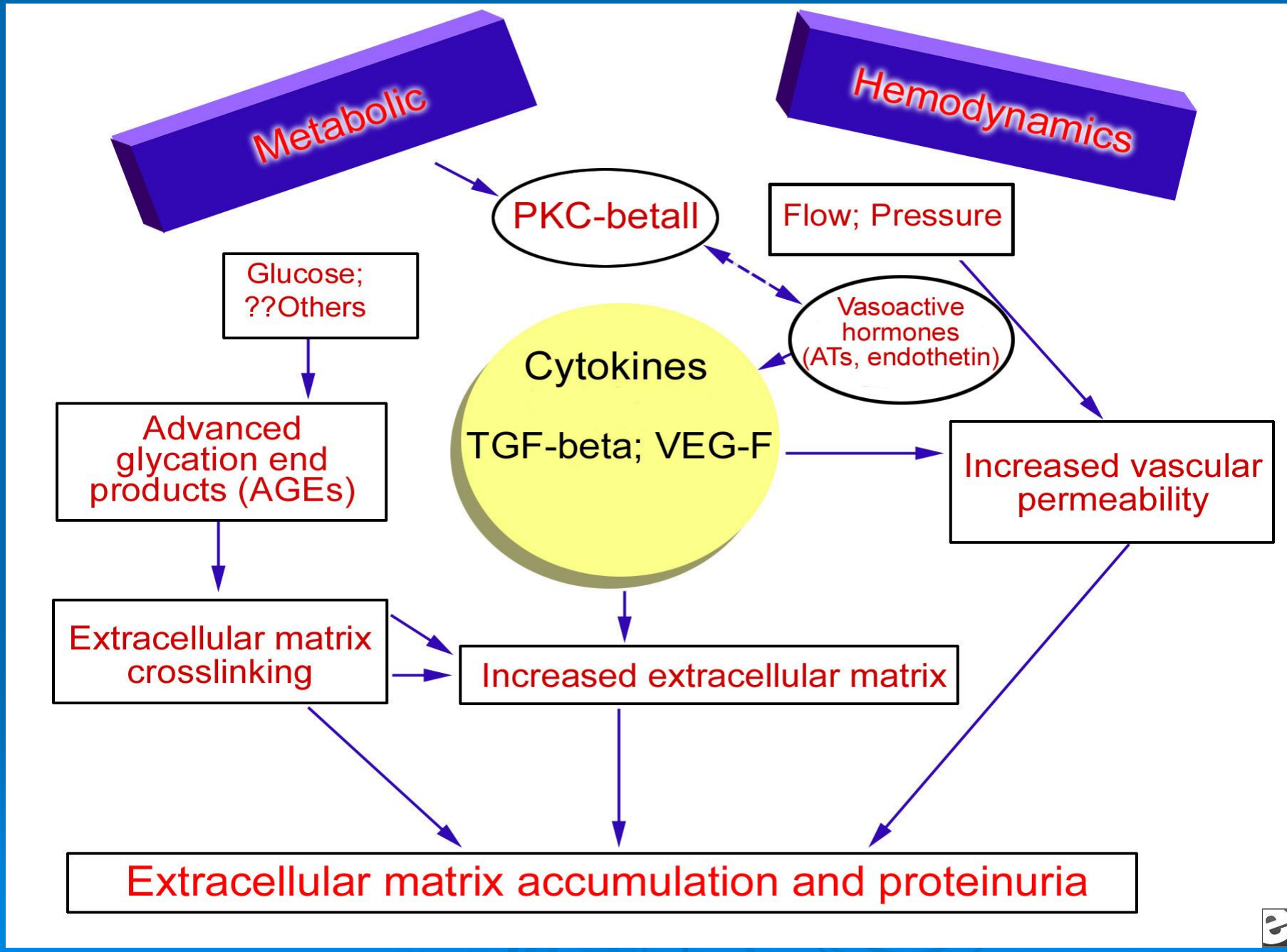
Pathogenesis of diabetic nephropathy:

-**Genetic factors** – connection to hypertension, increase in activity of Na-Li cotransport, abnormalities of RAAS

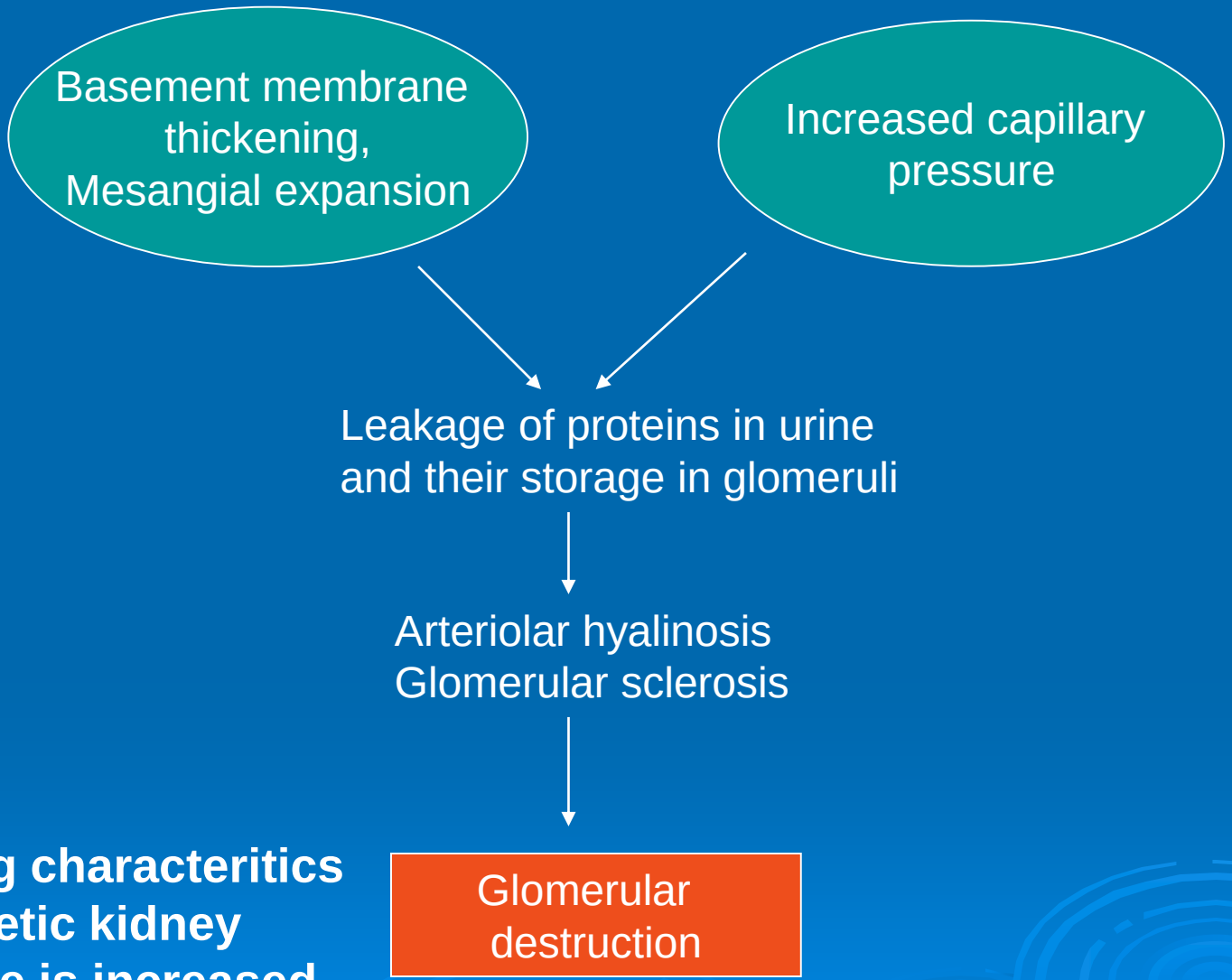
-**Hemodynamic changes** – ↑glomerular blood flow caused by PG, EDRF (= cytokines)

-**Infuence of chronic hyperglycemia** – on hemodynamics, influence of nonenzymatic glycosylation, sorbitol´s path, oxidative stress

= DN is a result of long-term bad metabolic control in connection to genetic predisposition for hypertension

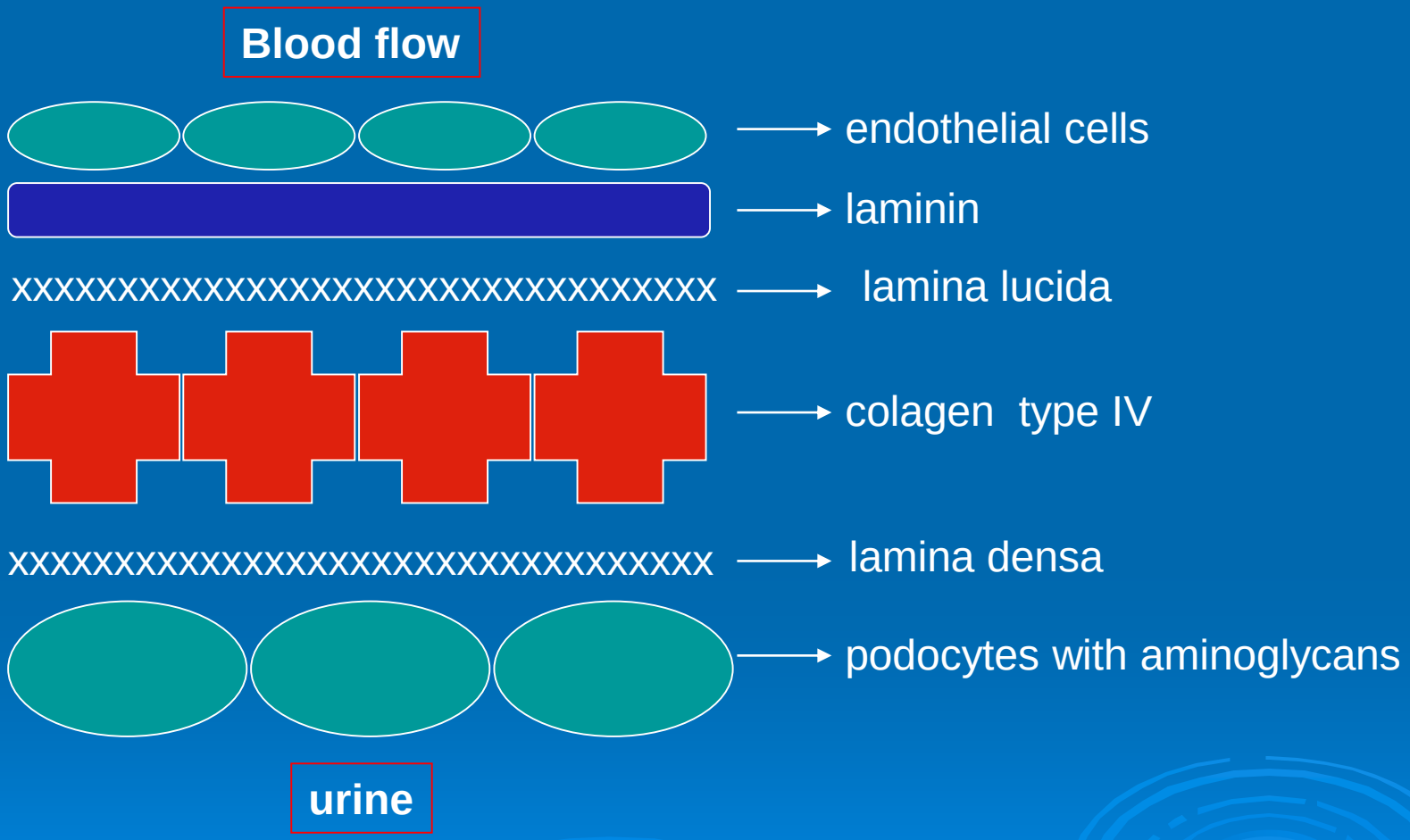

Metabolic
Hemodynamics
PKC-betall
Flow; Pressure
Glucose;
??Others
Vasoactive
hormones
(ATs, endothetin)
Cytokines
TGF-beta; VEG-F
Advanced
glycation end
products (AGEs)
Increased vascular
permeability
Extracellular matrix
crosslinking
Increased extracellular matrix
Extracellular matrix accumulation and proteinuria

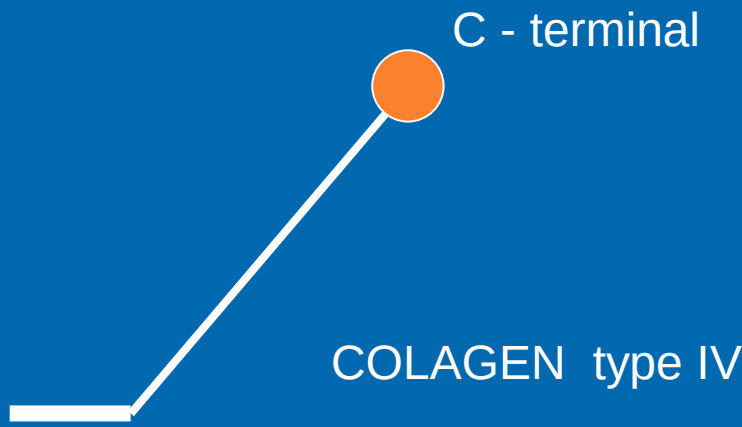
Morphological changes in DN :



leading characteritics ff diabetic kidney disease is increased permeability of basement membrane

GLOMERULAR BASEMENT MEMBRANE STRUCTURE

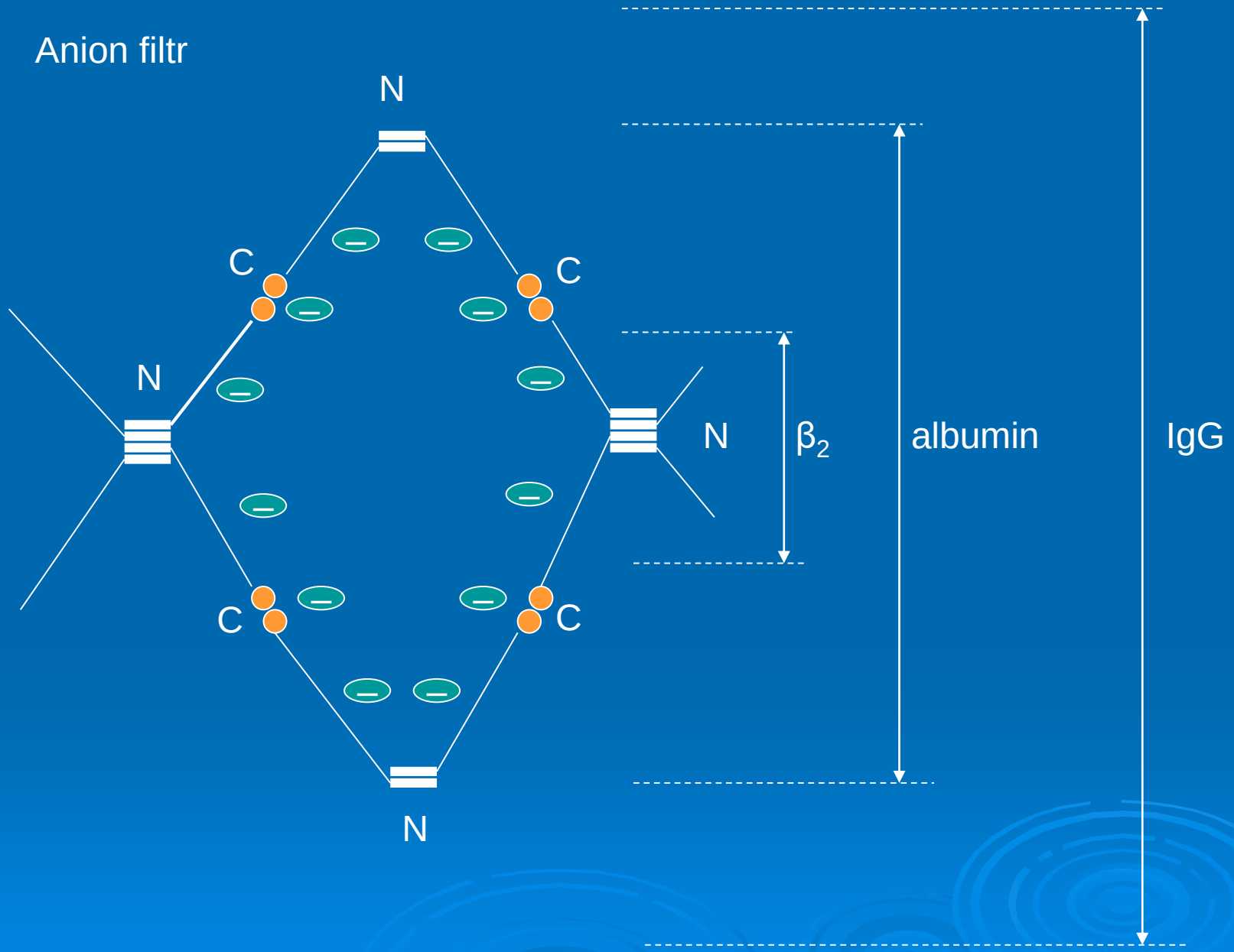




COLAGEN type IV

LAMININ

HEPARANSULFATE
(most negative charges)


Anion filtr
N
C
C
N
N
C
C
N
β2
albumin
IgG

The selectivity of proteinuria depends on structural changes of the glomerular basement membrane
-Just functional changes (diminished negative charge) = selective proteinuria = albuminuria
-Structural changes = non-selective proteinuria

Clinical presentation: leading signs are :
-persistent proteinuria
-decrease in renal function
-increase of blood pressure

I.stadium = silent

Ia hypertrofic-hyperfunctional, appears after ~ 0-2 years of diabetes duration, is charakterized by enhanced glomerular filtration rate and kidney hypertrophy present in ultrasound imaging

Ib stadium – microskopic changes, appears after ~2-5 years of diabetes duration – thickening of glomerular basement membrane, reversible

II.stadium = incipient nephropathy – appears after ~ 5-10 years of diabetes duration

IIa revesible microalbuminuria < 45ug/min

IIb irreversible microalbuminuria > 45ug/min

III.Stadium : overt nephropathy – proteinuria >0,5g/24hod, occurs after ~ 15-20 years of diabetes duration means progressive decline in glomerular filtration rate ~ 1ml/min/monthly

Due to protein leakage into urine the nephrotic syndrome can occur even before renal failure develops protein leakage to 10-20g/24hod

IV.Stadium : renal failure –

Decline in renal function

-Overt diabetic nephropathy rarely develops before 10 years' duration of IDDM.

- Approximately 3% of newly diagnosed NIDDM patients have overt nephropathy.
- The peak incidence rate (3%/y) is usually found in persons who have had diabetes for 10-20 years,
- The risk for the development of diabetic nephropathy is low in a normoalbuminuric patient with diabetes' duration of greater than 30.
- Patients who have no proteinuria after 20-25 years have a risk of developing overt renal disease of only approximately 1% per year.

Clinical presentation :

1/ changes in renal function: GFR reduction, metabolic acidosis, renal osteopathy..

2/ changes in metabolic control:

- diminished insulin degradation in renal tubular cells – the half-life of insulin is prolonged
- impairment in OADs degradation (sulfonylurea) – **hypoglycemia!!!!**
- increased insulinresistance
- impairment of gluconeogenesis and glycogenolysis in liver
- lipid levels abnormalities

3/ vascular complications – in renal failure the course of vascular complications accelerates

Increased basement membrane permeability in kidneys reflects the impairment in endotelial function generally – a marker of risk of cardiovascular disease!

Management of DN : speed, timeliness and AGGRESIVITY!

-Metabolic control

-**Blood pressure control** – antihypertensive treatment

-Target BP < 125/75 mmHg

-„Restricted“ protein diet 1g/kg/day – not to stimulate glomerular hyperfiltration

-Urinary tract infection treatment

Renal failure: the same treatment, no difference from the rest of RF

Fluid bilance

Low protein diet - 0,6g/kg/den

Blood pressure control

Ca++ disturabnces treatment, alcalization, anemia treatment (EPO)

Renal function replacement : Kidney Tx or Kidney/pancreas Tx

peritoneal dialysis

haemodialysis

Diabetic neuropathy

- Difuse non-inflammatory damage of peripheral nerves function and structure funkce (motor, senzitive, autonomic)
- Pathogenesis: metabolic theory (hyperglycemia – polyol´s path), vascular theory (ischemia vasa nervorum), autoimmune theory
- Neurophysiology: loss (or decrease of speed) of impuls conduction
- Prevalence 7,5% at diabetes onset and 50% after 25 years of diabetes duration

1/ Peripheral (somatic) neuropathy:

-**Symetrical** – distal sensory-motor, autonomic neuropathy
-**Focal, multifocal neuropathy** – radiculopathy, mononeuropathy, strait neuropathies, cranial neuropathies (n.III,IV,V,VII)

Clinical presentation:

-Nerve irritation – sensations of shivering, burning, creeps, freezing
-Loss of sensations
-Motor function disturbances

Treatment: causal treatment does´nt exist.
Metabolic control, insulin therapy, vitamins

2/ Autonomic neuropathy – clinical presentation:

Cardiovascular: diminished oscillation of heart rate
„sinus arytmia“, ortostatic hypotension

GIT – diabetic gastroparesis, diabetic enteropathy

Urogenital system – neurogenic bladder, erectile disturbances

Disturbances in insulin contraregullatory hormon secretion
Hypoglycemia unavareness

Diabetic foot syndrome

- 15 – 25% diabetic patients during their life
- ***Serious sequelae -*** gangrena (20x more)
- Necessity of ***amputation*** (30x more)

ETHIOLOGY:

- diabetic ***neuropathy***
- diabetic ***angiopathy*** (tissue ischemia)
- ***limited joint mobility***

- ***Infection*** limits the ulcer healing

1/ Inspection:

Systematically inspect both feet and compare them

- Skin – colour, quality, damage, cracks, nails, hair

Inspection:

Systematically inspect both feet and compare them

- Hyperceratoses
- swelling, lymfedema, gout…

Inspection:

Systematically inspect both feet and compare them

Deformities:

- Hammer toes
- Halluces valgi
- Metatarsal head area disturbancies
- Charcot foot

2/ Palpation:

Systematically palpate both feet and compare them

- ***Skin temperature*** – inflammation, fracture, Charcot foot
- ***puls*** – ATP, ADP

3/ Neurological

- Pains, parestesias
- Loss of sensations
- Tunning fork/biothesiometr
- Monofilaments
- Warm/cold sensation

Macrovascular complications of diabetes mellitus :

- Diabetic macroangiopathy = atherosclerotic manifestation in marginal arteries
- Most serious cause of mortality and morbidity of diabetic patients
- Stenoses or obliterations of arteries – dominished blood flow

Atherosclerosis in diabetic patients

- 2 – 4x more frequent
- Women are affected as well, no physiological protection
- Presentation earlier and in a more progressive way in comparison to non-diabetic patients
- More difuse affection, smaller arteries are affected
- Risk cummulation (IR, dyslipidemia, hypertension, AGEs…)

Clinical presentation of atherosclerosis:

- Coronary heart disease (CAD)
- Peripheral arteries disease (PAD)
- Brain tissue ischemia

Cardiovascular disorders are the leading cause in diabetic mortality - ¾

The CAD mortality is 2 – 3x higher

Heart failure presentation 2 – 3x more frequent

Silent MI more frequent

Hypertension:

- Often occurs in diabetic type 1 + 2
- DM 1 : secondary x primary
- DM 2 : primary, often before DM dg, prevalence 40 – 80%.
- Hypertension management : non-drug therapy, low salt diet, exercise, antihypertensive drugs (1st choice ACEI)